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TITLE: Evaluation of Neurophysiologic and Systematic Changes during Aeromedical Evacuation and en Route Care of Combat Casualties in a Swine Polytrauma

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14. ABSTRACT

There is a dearth of knowledge about the effects of long range aero-medical evacuation on injured organs, as well as an emerging published database suggesting clinically significant adverse effects of hypobaria on even healthy tissues. Cabin pressure is equivalent to an altitude around 8,000ft. at which inspired oxygen is sufficient to maintain blood oxygen saturation above 90% in a healthy individual. In combat casualties with multiple injuries this could however compromise oxygen delivery and result in hypoxemia. Additionally, increase in altitude with concomitant decrease in atmospheric pressure allows gas expansion in body cavities. The volume of trapped gas expands by approximately 35% from sea level to an altitude of 8,000 feet. This can expose already vulnerable patients to severe complications. In light of this, a thorough investigation of the effects of hypobaria in clinical settings simulating the most important injury patterns encountered by combat casualties is necessary to optimize treatment efficacy and safety.

During the third year of this project, experiments in swine with Acute Respiratory Distress Syndrome (ARDS) and with Traumatic Brain Injury (TBI) have been completed and results have been presented at National Scientific Meetings. We found that a simulated four hour aeromedical evacuation flight in those models significantly reduced arterial oxygen pressure and increased intrapulmonary shunt fraction in ARDS and significantly reduced cerebral perfusion pressure and brain tissue oxygenation in TBI compared to normobaric conditions. Further studies are indicated to simulate other en route care scenarios and possibly revise casualty evacuation guidelines.

15. SUBJECT TERMS
Aeromedical evacuation, en-route care, hypobaric conditions, hypobaric chamber, swine model

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Table of Contents

INTRODUCTION:

Rapid evacuation of combat casualties to definitive care in the United States is practice based on evidence derived from recent military conflicts and has greatly diminished morbidity and mortality among combat casualties. However, not much is known about the effects of long range aero-medical evacuation in hypobaric environments on the physiology and organ function of injured warfighters, thus potentially and unknowingly putting combat casualties at risk during evacuation. Traumatic brain injury (TBI) patients are of particular concern, since small changes in ambient conditions such as cabin pressure and temperature could potentially have detrimental effects on the already vulnerable brain. There is evidence that hypobaria as well as in-flight cabin pressure fluctuations can induce neurological symptoms in otherwise healthy persons due to altitude decompression sickness. This suggests that high altitude hypobaric conditions can have detrimental effects on pulmonary and neurologic outcome and that aero-medical conditions and/or therapeutics can be optimized to attenuate such adverse effects.

Our hypothesis is that hypobaria during simulated long-range aero-medical evacuation has adverse effects on brain blood flow and tissue oxygenation, as well as lung function in swine models of neurotrauma and polytrauma. We plan to investigate the effects of aero-medical evacuation on neurophysiology and lung function in swine models of TBI with and without hemorrhagic shock (HS) and/or ARDS (polytrauma).

BODY:

The following two tasks were initiated in Year 3 of the grant and continued during this reporting period of year 4:

Task 3. Animal experiments during normobaric conditions (months 5-28):
Subtask 1. Complete 72 animal experiments in Sham, TBI alone, TBI+HS, ARDS alone, TBI+ARDS and TBI+HS+ARDS groups. Animals will be randomized (months 5-28)
Subtask 2. Hematologic and hematologic analysis of blood samples (months 5-28).
Subtask 3. Necropsy, gross pathology, histopathologic analysis (months 5-28).

Task 4. Animal experiments during hypobaric conditions (months 15-39):
Subtask 1. Complete 10 pilot animals to test hypobaric chamber and animal set up for monitoring within the chamber (months15-16).
Subtask 2. Complete 72 animal experiments in Sham, TBI alone, TBI+HS, ARDS alone, TBI+ARDS and TBI+HS+ARDS groups. Animals will be randomized (months 17-39)
Subtask 3. Hematologic and hematologic analysis of blood samples (months 17-39).
Subtask 4. Necropsy, gross pathology, histopathologic analysis (months 17-39).

Task 5. Data analysis and publication (months 40-48):
Subtask 1. Quality control of databases and lock databases (months 40-42)
Subtask 2. Statistical analysis (month 43-44).
Subtask 3. Final Study report preparation (months 45-47).
Subtask 4. Manuscript preparation and submission to peer-reviewed journal (months 46-48).

Please note that due to unforeseen animal health issue we had to halt experiments before the end of this grant. We received a one year no cost extension to complete the animal work.

KEY RESEARCH ACCOMPLISHMENTS:

1. Animal experiments with TBI+Acute Respiratory Distress Syndrome (ARDS) have been completed:

Anesthetized swine had fluid percussion TBI and ARDS was induced bronchoalveolar lavage, followed by injury-specific in-hospital care over two hours. Once the animal was stable, a 4 hour aeromedical evacuation was simulated in a hypobaric chamber with atmospheric pressure equivalent to an altitude of 8000 ft. (HYPO, n=6). Control animals were kept at normobaric (ground transport) conditions (NORMO, n=6). Animals were intubated and ventilated with 40% O_2. At 6 hours, animals were euthanized and a full necropsy was performed. Systemic physiology data (vital signs, pulmonary artery catheter parameters, lung function) was collected and blood was analyzed for blood gases, electrolytes and organ function assay indicators.

2. Animal experiments with TBI+HS have been completed:

Anesthetized swine had fluid percussion TBI and a 40% estimated blood volume controlled hemorrhage and injury-specific care over 2 hours, followed by a 4 hour aeromedical evacuation simulated in a hypobaric chamber with atmospheric pressure equivalent to an altitude of 8000 ft. (HYPO, n=6). Control animals were kept at normobaria (NORMO, n=6). At 6 hours, animals were euthanized. Systemic and neurophysiology [brain tissue oxygenation ($pbrO_2$)] data were collected. Blood was analyzed for arterial gases and electrolytes

3. Animal experiments with TBI+HS+ARDS are currently ongoing:

Anesthetized swine had fluid percussion TBI and a 40% estimated blood volume controlled hemorrhage and ARDS. After injury-specific care over 2 hours, animals were then exposed to a 4 hour aeromedical evacuation simulated in a hypobaric chamber with atmospheric pressure equivalent to an altitude of 8000 ft. (HYPO). Control animals were kept at normobaria (NORMO). At 6 hours, animals were euthanized. Systemic and neurophysiology [brain tissue oxygenation ($pbrO_2$)] data were collected. Blood was analyzed for arterial gases and electrolytes.

4. Histopathological analysis of all sub studies is currently ongoing.

5. Preparation of manuscripts for peer-reviewed publication currently ongoing.

REPORTABLE OUTCOMES:

Steve Chun, MD; Ashraful Haque, MD; Brittany Hazzard, BS; Saha Biswajit, MD, Martin Harssema, MD, Charles Auker, MD, PhD2, Debra Malone, MD, Richard McCarron, PhD; Anke Scultetus, MD: "Brain hypoxia is exacerbated in hypobaric conditions during aeromedical evacuation in swine with traumatic brain injury". Eastern Association for the Surgery of Trauma Annual Meeting, San Antonio, TX, January 2016.

Anke Scultetus MD; Ashraful Haque, MD; Brittany Hazzard, BS; Saha Biswajit, MD; Steve Chun, MD; Martin Harssema, MD; Charles Auker, MD, PhD; Debra Malone, MD; Richard McCarron, PhD: "Effects of long-range aeromedical evacuation on TBI in a swine model". Military Health System Research Symposium, Ft. Lauderdale, FL, August 2016.

Scultetus AH, Haque A, Chun SJ, Hazzard B, Mahon RT, Harssema MJ, Auker CR, Moon-Massat P, Malone DL, McCarron RM: Brain hypoxia is exacerbated in hypobaria during

aeromedical evacuation in swine with traumatic brain injury. J Trauma Acute Care Surg. 2016 Jul;81(1):101-7.

CONCLUSION:

In this swine polytrauma model of TBI+ARDS, hypobaria during simulated aeromedical evacuation decreased brain tissue oxygenation over time compared to normobaric ground transport conditions. There were no differences in partial pressure of arterial oxygen or oxygen delivery, extraction and consumption data. This suggests that in this particular model, ARDS was not a likely contributor to decreased PbtO2 in HYPO animals. This is further supported by similar data trends in our earlier TBI alone study.

In this swine polytrauma model of TBI+HS, prolonged hypobaria resulted in adverse systemic and neurologic physiology despite stable arterial partial pressures of oxygen. Particular attention needs to be given to casualties two hours into flight. Flight duration appeared to affect the stability of the patient and could be potentially detrimental for TBI and HS patients.

Further studies are indicated to simulate other *en route* care scenarios and possibly re-evaluate casualty evacuation guidelines.

REFERENCES:

None.

APPENDICES:

None.

SUPPORTING DATA:

TBI+ARDS Experiments:

Baseline parameters were similar in both groups during the in-hospital phase and at the beginning of flight.

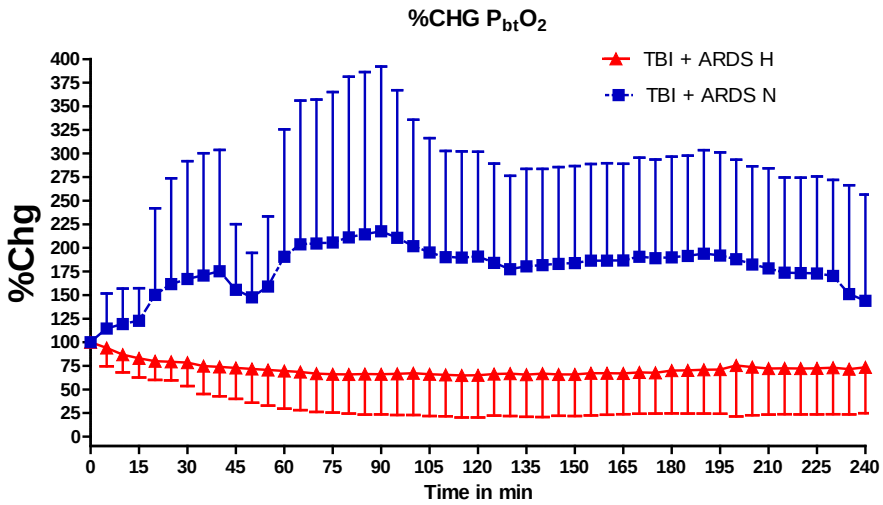


Figure 1: Percent change of Partial pressure of brain oxygen ($PbtO_2$) showed a decrease in brain oxygenation in the HYPO compared to NORMO group.

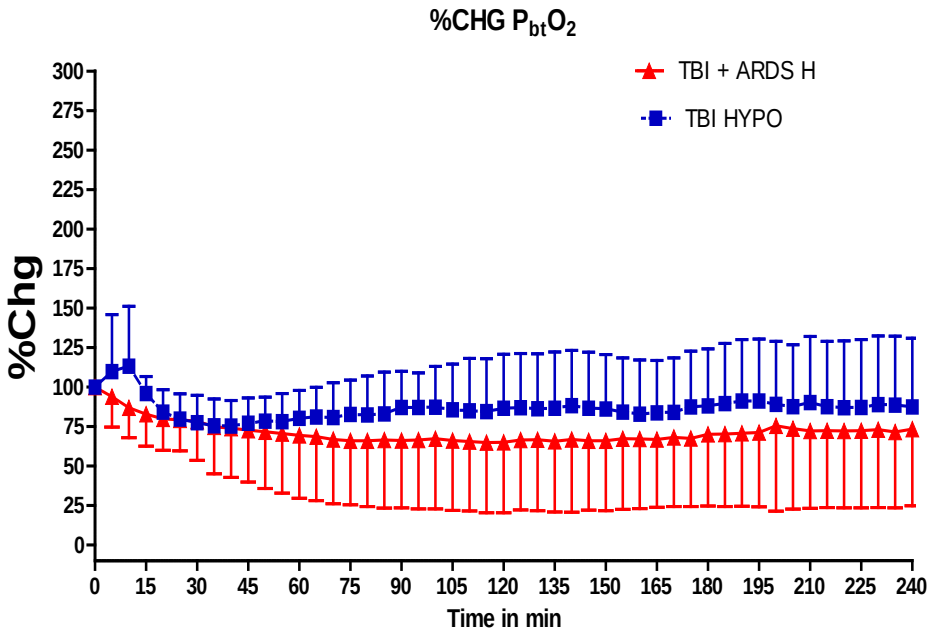


Figure 2: Interestingly, when comparing PbtO2 in the TBI alone group to the TBI+ARDS group, there was a similar trend in HYPO animal to reduced brain tissue oxygenation, suggesting that ARDS is not a significant contributor to the decrease in brain oxygenation.

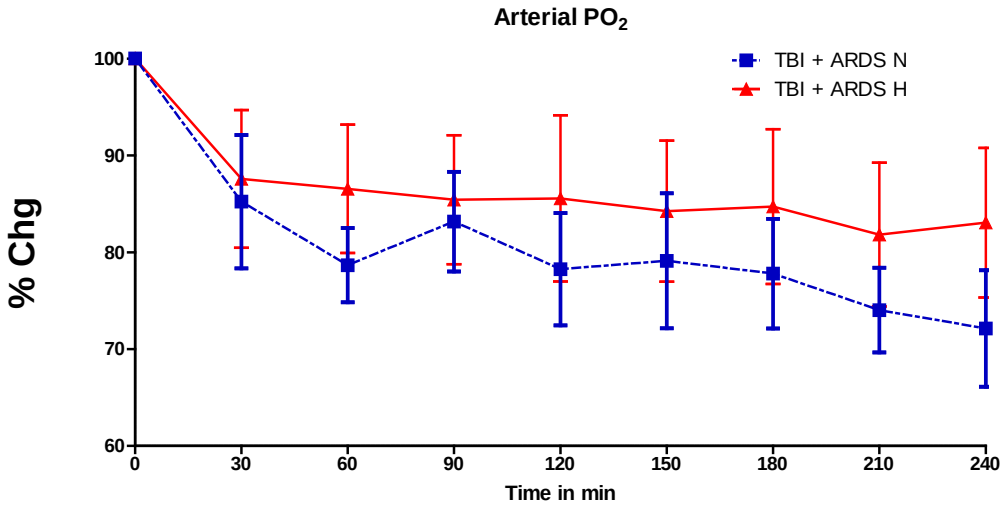
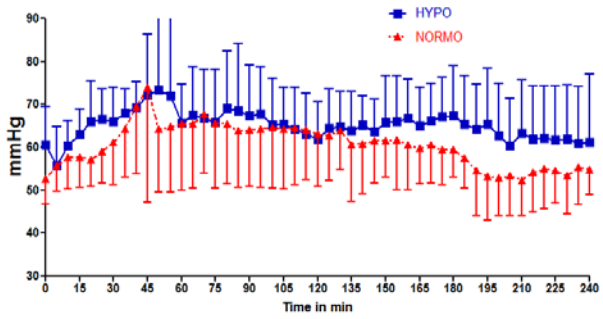


Figure 3: Arterial PO_2 (shown as percent change from beginning of flight) was not significantly different between HYPO and NORMO groups.
VO_2 (O_2 consumption), DO_2 (O_2 delivery), O_2ER (ratio between consumption and delivery), CaO_2 (arterial O_2 carrying capacity), and Qs/Qt (Shunt ratio) showed no differences between groups.

TBI+HS Experiments:

Baseline parameters were similar in both groups during the in-hospital phase and at the beginning of flight.

Mean Arterial Pressure (MAP)



Mean Pulmonary Artery Pressure (MPAP)

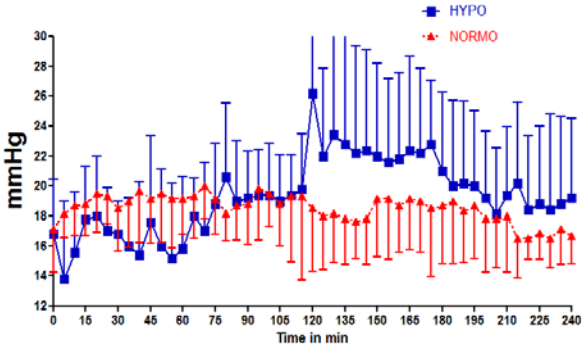
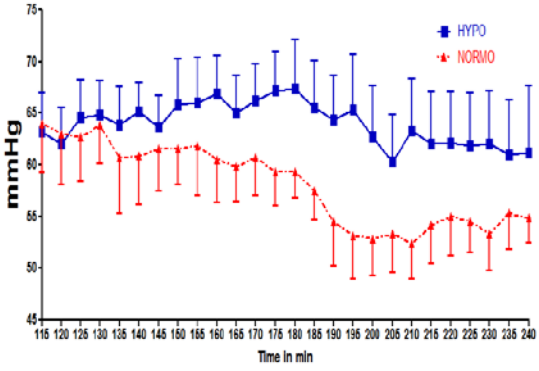


Figure 4: There was no statistical difference between groups in MAP and MPAP during the 4 hour evacuation period.

Mean Arterial Pressure (MAP)



Mean Pulmonary Artery Pressure (MPAP)

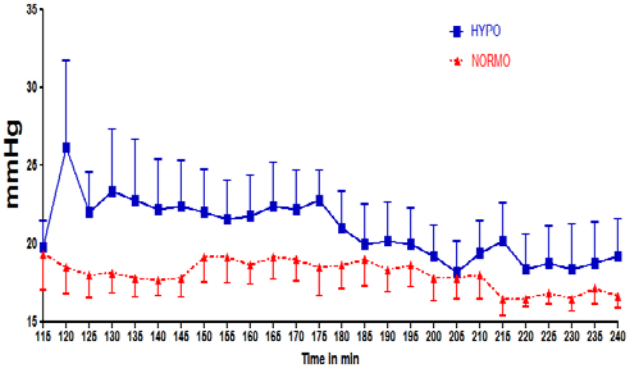


Figure 5: However, a subsequent analysis of data from T115 to T240 showed significantly reduced MAP ($p \leq 0.01$) and MPAP (≤ 0.05) in HYPO animals. This data aligns with clinical in flight observations reported by Critical Care Air Transport (CCAT) personnel.

Partial pressure of brain oxygen (PbtO2)

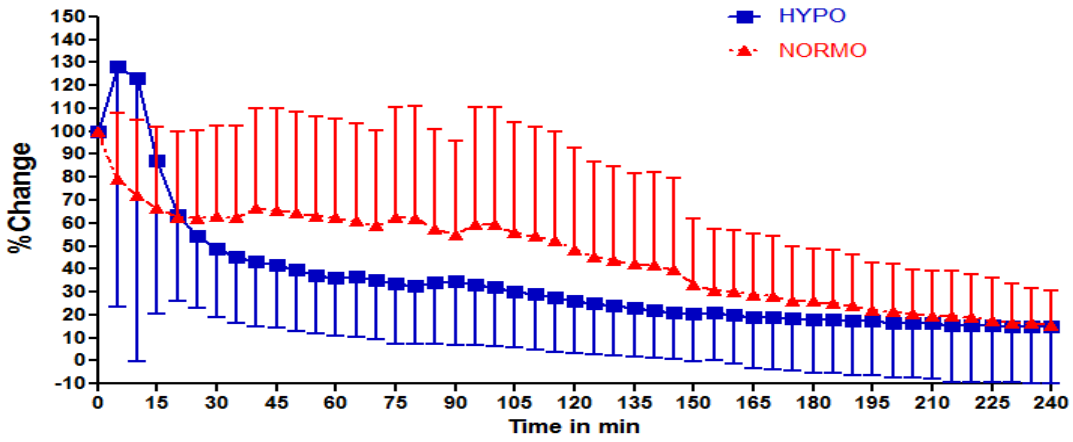


Figure 6. Brain tissue oxygenation in HYPO animals was significantly lower than in NORMO animals ($p \leq 0.05$).

Lactate (LAC)

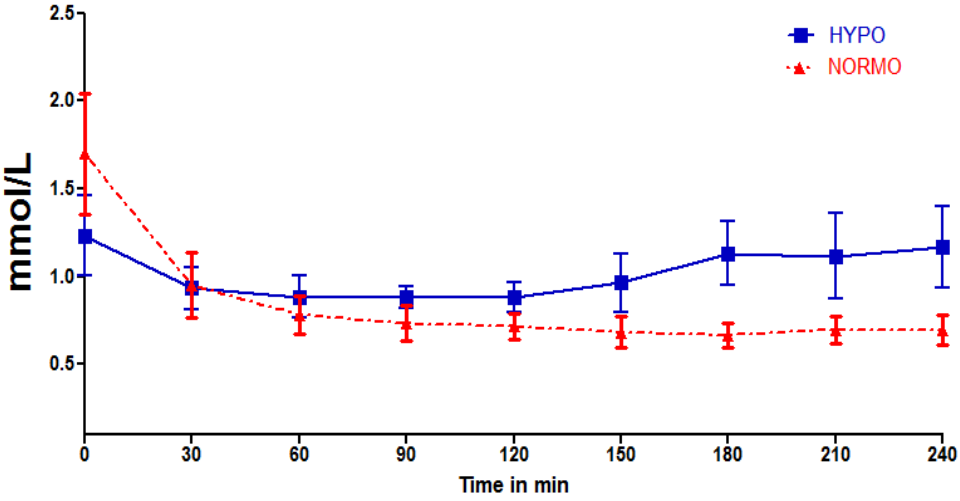


Figure 7: Lactate steadily increased in the HYPO group over time ($p \leq 0.01$).